I have removed the sac in all cases.

I attached great importance to placing the ligature high up on the neck of the sac. In many cases of inguinal hernia I fastened one loose end of the sac-ligature to the internal oblique and inner pillar of the ring; but I doubted the value of it. In almost all instances of inguinal hernia I brought together the pillars of the ring by sutures, at the same time avoiding any pressure on the constituents of the spermatic cord. I have employed for sutures and ligatures prepared catgut, kangaroo-tail tendon, and silk. I give the preference to silk as more durable and reliable.

In the treatment of the femoral hernia I contented myself with ligature of the sac at its neck and its abscission.

PERNICIOUS MALARIAL FEVER.

By George Dock, M.D.,
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In the modern study of malaria, etiology and diagnosis have progressed much more rapidly than pathology. The discovery of the parasites by Laveran destroyed the elaborate and often ingenious explanations of the phenomena of the disease which had been formulated up to that time, and the recognition of the fact that in the earlier anatomical studies the parasites were not accurately observed made it obvious that the histological lesions must be re-studied. Malarial diseases differ from most infectious diseases in that although the infection is always and only in the blood—is, in an old and still used sense, general—yet the clinical features vary to a marked extent in different cases. It must be clear that in the new study of malaria many single observations must precede a complete survey of the subject. In the following pages I present the results of the study of a limited material. I have devoted most space to the study of a single case which offered unusual advantages in several respects, especially in the previous health of the patient and the short and severe course of the infection. The older writers had a very extensive list of varieties of pernicious malaria for the purpose of expressing briefly the salient features of different cases. As usual in such cases, one name does not always suffice, so that in my own case one might be in doubt whether to call it hæmaturic, remittent, gastric, or dyspnœic. Looked at from the modern standpoint, we should ascribe chief importance to a feature the older terminology did not include, viz., the rapid destruction of red blood-corpuscles. I have given the history of this case rather in detail. The rest of my material was derived from a case of algid pernicious malaria without unusual features, and two cases of malaria of milder type in which death occurred from accidental rupture of the spleen.[1] I have also used the liver of an old case of malaria preserved in the Pathological Institute of the University of Leipzig.

The points of special importance exhibited in this case are the enormous development of the parasites and consequent anæmia and melanæmia; the parenchymatous degeneration and inflammation in liver, kidneys, and stomach; the thrombosis in various organs; a remarkable condition of the blood in the abdominal fatty tissue, and finally, the micro-chemical examinations of the tissues.[2]

Acute malarial infection; remittent fever, emesis, dyspnœa, hæmaturia, and delirium; death on the seventh day, from failure of respiration. Post-mortem: Melanæmia; thrombosis; necrosis and inflammation of liver, kidneys, and stomach; hyperplasia of spleen and lymphatic glands, etc. G. P., aged twenty-three years, born in England, emigrated to America in 1890. Landing in Galveston, Texas, he worked for a few weeks on vessels in non-malarial localities. In August, 1890, he took a position on a steamer plying between Galveston and San Jacinto, Texas, a place where the most severe forms of malarial disease occur. P. made weekly trips to San Jacinto, remaining there from two to four days, and, the weather being warm, slept on deck, close to the shore. Up to October 25th, P. was in perfect health, never having been ill in his life. On the day named, on the trip to Galveston, he felt pain in the abdomen, and slight nausea. These symptoms passed away, and he slept well the following night. Next day, about 10 o'clock A.M., he had headache and a slight chill, followed by fever and sweating. From that time he thought he had fever constantly, but without chills and sweating. On the 27th he vomited without obvious cause. Appetite remained fairly good. On the 30th, on account of the constant fever and increasing weakness, P. sought admission to the hospital. He had taken no medicine but a cathartic pill, which had a mild effect. At 5 P.M. the same day the following *status* was taken:

"Man of medium size, well developed and well nourished. Mind clear, but slightly excited. Complains of constant severe pain in the frontal region and in the back and legs. The skin is pale and dry. There is no jaundice. There are recent herpes vesicles on the lips. The tongue is swollen and indented, with a gray coating. At rare intervals patient vomits bile-stained, mucous, watery fluid. The bowels are confined. Splenic dulness extends from the eighth rib three fingerbreadths beyond the costal margin. The splenic region is sensitive to pressure; the spleen can be felt, but is very soft. There is marked tenderness in the epigastrium. The liver is not distinctly enlarged. Temperature (5 P.M.), 100° F.; pulse, 88."

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[1] University Medical Magazine, vol. i. p. 469.

[2] The later examinations were made in the Pathological Laboratory of the University of Leipzig, and I wish to thank the Director, Professor Birch-Hirschfeld, for giving me the freedom of the Laboratory and for many other kindnesses, and to thank the assistants, Privatdocent Dr. George Schmorl and Dr. Richard Kockel, for valuable assistance. I am especially indebted to Dr. Schmorl (whose reputation for unexcelled work in photo-micrography is well established) for the negatives from which the accompanying figures have been made.

The examination of the blood, which at once revealed a severe malarial infection, will be described later.

During the next twelve hours the patient took thirty grains of quinine, in solution, by the mouth, without symptoms of cinchonism.

The patient's condition remained about the same until noon the next day, when a sudden change for the worse was observed. The pulse was weak, from 150 to 160 to the minute. Severe and uncontrollable vomiting set in. Neither medicine nor food could be retained, and even attempts to swallow bits of ice or carbonated water caused violent retching. Later delirium came on, at first mild and voluble, later somewhat wild. The temperature, which had ranged between 99° and 101°, rose suddenly, reaching 104.8° at 3 P.M. It then fell slowly to 103.6° at 6 P.M., and remained stationary until death. During the afternoon dyspnœa appeared and became more and more severe, so that if the patient attempted to rise he would fall back exhausted. Finally, at 8.15 P.M., breathing ceased, the heart beating for several minutes later.

On the day of admission, through some oversight, the urine was not saved. The next day none was passed, so that at 6 P.M. a catheter was introduced and about 30 c.c. of urine obtained. This was yellow, with a pinkish tint; showed a marked turbidity with rapidly falling brown granular sediment. Albumin was present to the amount of one-tenth the bulk on standing. The sediment was made up of numerous casts, most of them of large size, but a few were narrow and short. All were of brown color. The larger ones were made up of epithelial cells, leucocytes, well-preserved red blood-corpuscles and "shadows," and brown and yellow detritus granules. The small casts were sometimes similarly made up, sometimes smooth and waxy-looking. There were also many free red blood-corpuscles and renal epithelial cells, and oxalate and uric acid crystals. The epithelial cells were brown, but otherwise of normal appearance.

The *autopsy* was made twelve hours after death. The skin was pale and slightly jaundiced. Rigor mortis was marked.

On removing the calvarium, the membranes showed unusual anæmia. The sinuses contained tough gray clots. The brain was anæmic, not œdematous, of firm consistence. The white substance had a faint grayish tint, otherwise there were no macroscopic alterations in the brain or other parts as far as the beginning of the cord. The latter was not removed.

The heart was of normal size, the muscle anæmic, pale yellowish-brown, soft. In both ventricles were firm fibrinous clots of pale grayish color.

The lungs were in the inspiratory position, very anæmic, otherwise of normal appearance.

The spleen was greatly enlarged, weighing 675 grammes. The capsule was smooth in general, but had soft, easily separable adhesions to the peritoneum in the region of the eleventh rib. The tissue was very soft, having the consistence of thick cream. Section was dark red or chocolate colored, Malpigian bodies not distinctly visible.

The kidneys were of normal size, the capsules stripping readily. The cut surface was anæmic, pale grayish-red in the cortex, pale red in the pyramids. The adrenals of normal appearance.

The bladder contained 50 c.c. of urine having the same microscopic and macroscopic and chemical peculiarities as that examined during life.

The stomach was greatly distended and contained two litres of greenish fluid. The mucous membrane was very thick, of dark-gray color, and covered with tough, adherent mucus. In the fundus were a few small ecchymoses.

The upper part of the small intestine showed nothing abnormal, but in the lower part of the ileum the Peyer's patches and solitary nodules were enlarged and dark gray. The colon showed no change.

The liver was slightly enlarged, the surface smooth, dark greenish-gray. Section showed a similar color; the tissue was very anæmic, cloudy, slightly swollen; the acini not distinct. The gall-bladder and ducts showed no abnormality.

The pancreas was anæmic and gray.

The mesenteric glands were enlarged, soft, and œdematous. The fat in the abdomen was remarkable for its gray color. The muscles in general were dry and dark red.

The bone-marrow (vertebræ, sternum, and ribs) was dark red, but anæmic.

Pieces of various organs were placed in absolute alcohol. Fresh preparations of various tissues were examined in normal salt, and in Müller's solution.

The examination of the blood. During life the blood was examined in the ordinary way, by taking a drop from the cleaned finger-tip and examining, at the bedside, with a Zeiss $\frac{1}{12}$ in. oil-immersion lens. The notes made at the time have been controlled recently by the study of cover-glass preparations. The latter were fixed by heat, and stained with Loeffler's methylene-blue, or hematoxylin, and eosin.

October 30, 5 P.M. Blood-drop of normal appearance. Red and white corpuscles in normal proportions. Parasites are present in enormous numbers. Every field (containing sixty to eighty red corpuscles) contains a number, never less than two or three, often as many as twelve, fifteen, or eighteen. In one field of a dry preparation I have found forty. Frequently two parasites, sometimes three, can be seen in one corpuscle. The parasites are from one-quarter to one-third the diameter of a red corpuscle, when at rest, but usually they are in active amœboid motion. Some of them when at rest show a ring or seal-ring form, and contain extremely small, amorphous, brown or yellow pigment grains. Most of the organisms are roundish (not ring-shaped) at rest, appear homogeneous, and contain roundish dark-brown or black pigment masses in or near the centre. In some of the larger organisms, about half the diameter of a red blood-corpuscle, the earliest indication of segmentation can be seen, apparently, in the appearance of radial lines or streaks, or of small, dark areas around the pigment. Very rarely bodies can be seen which seem to represent the earliest stages of the crescents. These are long or oval, with scattered or central pigment grains, have very little motion and a different refraction from the others. In stained preparations small, round, deeply staining areas can often be made out in the organisms. In the fresh blood there were very few free parasites, and no crescents or flagellate bodies. There are a few polynuclear leucocytes with pigment, either in fine grains or larger, roundish, darker masses.

31*st.* 12 M. Blood dark-red. The red corpuscles are often irregular in outline or look as if broken, but without a tendency to crenation. The leucocytes are relatively slightly increased. Parasites numerous.

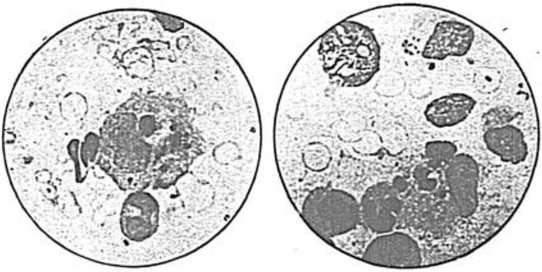
They are smaller than at the last examination, with no pigment, or very few small yellowish-brown granules. Pigmented leucocytes are more numerous than before.

5 P.M. The parasites are in the same stage as at this time yesterday, but are even more numerous. During the examination marked leucocytosis suddenly appeared, the proportion of white to red corpuscles being one to five.

A count of leucocytes shows the following proportion: large lymphocytes, 20 per cent.; small lymphocytes, 12.5 per cent.; large polynuclear, 22 per cent.; small polynuclear, 40 per cent.; transition and large mononuclear, 5 per cent.; eosinophile, less than 0.2 per cent.

It is necessary to explain that by the term "large polynuclear," I include not only the larger forms of that class, such as are found in healthy blood, but also large cells like the phagocytes in Figs. 1 and 2, the nuclei of which are usually simple but of irregular outline. Many of these cells, especially those with pigment, had in fresh blood a peculiar, hyaline appearance; sometimes their bodies were evidently broken down.

FIG. 1. FIG. 2.



FIGS. 1 AND 2.—Blood from the finger-tip fifteen minutes before death. Phagocytes with parasites in the stage just before segmentation, and pigment from fully segmented organisms. In the upper part of Fig. 2 is a phagocyte containing spores and a pigment-ball. Hæmatoxylin and eosin. Apochromatic obj. 3 mm., oc. 4. × 720.

Actual mitotic figures cannot be found in the leucocytes, but there are numerous cells having nuclei suggesting division, probably amitotic. (See the smaller cell in Fig. 1.)

An attempt to count the corpuscles was not successful. The blood was very dark and rather thick. With the Thoma-Zeiss instrument I counted, in several attempts, about 6,000,000 red corpuscles per c.mm., with variable proportions of leucocytes.

About this time nucleated red corpuscles appeared in the blood, but were only discovered in the stained preparations. They are all normoblasts with deeply staining nuclei, and are present in the proportion of about one to a thousand red corpuscles.

From five o'clock until eight the blood was examined continuously, and it was possible to follow the development of the parasites during that time. They became larger and less active, reaching finally a diameter equal to or slightly greater than half that of a red corpuscle. During the later phases the pigment became more and more closely aggregated, forming a roundish mass in or near the centre of the parasite. This stage can be seen in Figs. 1 and 2, taken from a preparation made at 8 P.M. In a preliminary report on this case (*Medical News*, May 30, June 6, 1891), I said that segmentation forms were not to be found in the peripheral blood. More extensive examinations have shown me that this is not so. In a dried preparation of finger blood taken just before death, stained with hæmatoxylin, I find five sporulation forms with central pigment free in the plasma, and four enclosed in phagocytes. (In Fig. 2, in the leucocyte at the upper part of the field, there is a group of spore-like bodies with a pigment-ball near by. This I have not counted as one of the four, all of which were more perfect.)

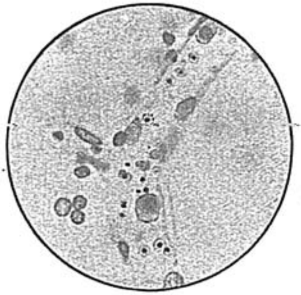
EXAMINATION OF THE TISSUES.—The alcohol hardening gave very good results in preserving the parasites. With suitable stains the organisms can be demonstrated with a clearness which leaves nothing to be desired. In order to show the relations of the parasite to the red blood-corpuscles sublimate fixation would no doubt have offered advantages; but for the parasites and the other tissues, alcohol can be recommended.

In staining, all kinds of nuclear dyes give good results. Alum-carmine stains the segmenting bodies and fully developed spores very well, and is useful in showing the relation of the pigment to the tissues. Hæmatoxylin, alone or with eosin as a contrast stain, I found on the whole most satisfactory. Methylene-blue gave good results in recently hardened tissues, but was not quite so useful in staining material long in alcohol. Figs. 3 and 4 show methylene-blue stains. Loeffler's solution was used, the sections remaining in it several hours and being rapidly washed in absolute alcohol and cleared in cedar oil. Safranin, fuchsin, and other aniline dyes did not give such good results as those mentioned.

In the following description I have limited myself, as far as possible, to the most important changes, leaving out many details, but omitting nothing essential.

Brain. In the brain the findings vary in different parts, as is usual in malaria. Immediately after the autopsy I examined the smaller vessels in the brain by pulling them out, with the membranes and plexuses, and examining by various powers. In this way it was easy to find the parasites, lying in rows or masses in the vessels. I paid special attention to the condition of the vessel walls and the possible presence of obstructions. But although I examined hundreds of vessels, evidence of thrombosis was scanty. Once I found a mass of parasites and leucocytes obstructing a small artery at its bifurcation. On the whole, the arterial and capillary walls were of normal appearance. In hardened sections the most important alterations are found in the cortex, where the smaller vessels are frequently full of, sometimes distended by, infected blood-corpuscles as shown in Fig. 3. (It must be remembered that only one plane is shown in the photograph; the capillary contains many times more than those which appear.) The smaller vessels in the cortex often show an excess of leucocytes, and in some of them there are thrombi containing parasites. The changes just described, though marked in some parts, do not appear on the whole to be so extensive as in some other reported cases. In the white substance the changes described are very uncommon. The larger veins are frequently distended with blood, though usually with few parasites. Thrombi are frequent, though rarely causing total obstruction. Many of the leucocytes in various parts of the brain contain pigment, sometimes parasites. The endothelial cells often contain minute glistening globules resembling hæmoglobin, and in the fresh preparations free globules of that kind were very common, though probably partly of post-mortem formation. In the central ganglia, the crura, pons, and medulla, the smaller vessels are empty; the larger veins show unusual fulness, but parasites are much less frequent than in the cortex. The upper part of the cord is anæmic, but a few infected red corpuscles can be found. The parasites in the brain are in the later stages, either in the fully segmented form or the spores lying loosely together. The brain and the cord, so far as examined, show no perceptible alterations of the tissue elements (alcohol hardening?).

FIG. 3.



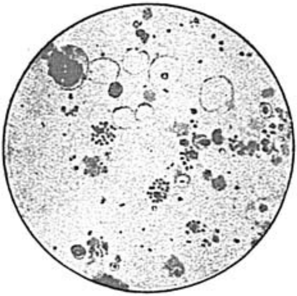
Capillary from brain cortex (3d left frontal convolution). Each pigment-ball is in the segmented body of a parasite, but the organisms do not show distinctly. Methylene-blue. × 720.

Heart. The muscle fibres show marked fragmentation, the transverse striation is well preserved; the nuclei of the muscles are frequently swollen. In the small arteries and capillaries are moderate numbers of parasites and of pigmented leucocytes. There is an increased proportion of leucocytes in the vessels, especially in the capillaries.

The clots from the ventricles consist of fibrin masses and leucocytes, with few red corpuscles. The large mononuclear leucocytes, or large lymphocytes, which are hard to distinguish in blood hardened *en masse*, are increased. There are also many large leucocytes with irregular nuclei, containing pigment grains and larger masses. The red corpuscles in the clots rarely contain parasites. Pigment and parasites are present in about the same proportions in clots from right and left ventricle, the proportions varying in different parts of the same clot.

Spleen. In scrapings of the spleen examined after the autopsy, parasites were found in enormous quantities, as shown by Fig. 4, from a cover glass preparation. The parasites were for the most part in the later stages, but in some places, in cover-glass preparations, small bodies can be seen, apparently in the red blood-corpuscles, which from their size and appearance seem to be bodies in the earliest stage of endoglobular existence. In fresh or cover-glass preparations the conditions as to pigment and other peculiarities are so much like those in the hardened tissue that a description can be omitted. Sections of the spleen show moderate hyperplasia of the lymphoid tissue with an intense hyperæmia which separates widely the elements of the pulp. Everywhere in the parenchyma, but varying in different parts, are enormous numbers of parasites. In some places every blood corpuscle contains one. They are almost all in the later stages. In consequence of the hardening, no doubt, the smallest forms, as found in the splenic blood and already described, do not show so well as in the cover-glass preparations. In the lymphoid tissue parasites occur at times in the capillaries. Here, too, are occasional pigmented leucocytes, but pigment grains are never to be seen in the lymphoid cells. Everywhere in the pulp there are large cells with relatively small nuclei. The bodies of the cells are irregular in outline, their nuclei rarely round, but usually bean-shaped, crescentic, or triangular. The cells always contain bodies of the following kinds, in varying number and proportion:

FIG. 4.



Splenic juice twelve hours post-mortem. Complete segmentation, and also several parasites in earlier stages, but with pigment massed in one ball. In sections the spores are never so numerous, being usually from ten to fifteen, whereas smear preparations show twenty or more. It would appear from this that division takes place in more than one plane. Methylene-blue. × 720.

1. Pigment in fine yellowish-brown grains, or in larger darker balls, like those in ripe parasites. Sometimes numbers of these balls can be seen apparently fused together. 2. Parasites with round bodies and central pigment, or segmented bodies. Sometimes the parasites can be recognized as being in the remains of red blood-corpuscles, sometimes not. In either case the parasites may be in a round clear area in the body of the phagocyte. 3. Leucocytes, with or without pigment. These are not uncommon, and sometimes one or two small or large lymphocytes can be seen in a large phagocyte. 4. Yellow, very minute globules resembling hæmoglobin. The number of enclosed bodies in these cells is sometimes almost incredible. It is not unusual to find as many as thirty of the large pigment-balls in one cell. Frequently they are so fused together as to make counting impossible. As many as twenty parasites may be seen in one phagocyte. The large splenic veins contain numerous pigmented leucoytes, and also many parasites, both in the red blood-corpuscles and free, as fully developed sporulating forms.

Lymph glands. The enlarged mesenteric lymph glands are hyperplastic and slightly hyperæmic. The capillaries contain pigmented leucocytes, rarely parasites.

The bone-marrow examined fresh contained many mature parasites and sporulation forms, either free or in leucocytes having the characteristics of macrophages. In the bone-marrow were unusually large numbers of the hyaline leucocytes already described.

Liver. The liver shows important changes of various kinds. There is a moderate degree of necrosis of the liver cells, shown by failure on the part of the nuclei to take stains, and a ragged and broken-down appearance of the protoplasm. In some areas without necrosis the nuclei are swollen. In a few places the protoplasm of the liver cells stains deeply with nuclear dyes and has an opaque appearance, resembling minute areas of coagulation necrosis. The necrotic areas are not symmetrical, nor have they any special localization, but are scattered over the acini. The portal connective tissue contains large numbers of small cells in its whole extent, most marked along the vessels of small or medium calibre. The cells are mostly round, of medium size, with round nuclei and narrow rim of protoplasm. A few are larger, with paler nuclei. These collections do not extend into the acini, but are sharply circumscribed laterally, though sometimes of great length.

All the intra-acinous capillaries contain pigment granules, which are so numerous as to simulate an injection when seen by low amplification. Examined more closely, one can see that the pigment is partly free in the plasma, partly in endoglobular parasites, and partly in leucocytes. The hepatic veins and portal veins frequently but not uniformly contain blood with parasites and pigmented leucocytes. The branches of the hepatic artery, when they contain blood, sometimes show pigmented leucocytes, but rarely parasites. The liver cells never contain pigment like that in the parasites. Almost everywhere, but especially in the portal zones, the cells contain numerous small yellow granules, with a more greenish tint than the usual liver pigment, which also occurs sparingly in the cells. Similar granules can also be found in the endothelial cells.

Kidneys. The capsules of Bowman are unchanged, but the capillaries of the glomeruli show loss of epithelium in some places, in others increase of nuclei. In various parts of the cortex there are small, ill-defined collections of small cells, usually near small bloodvessels. In various parts of the labyrinths the epithelial cells do not take nuclear stains; their protoplasm is granular, or sometimes greatly swollen or broken down, and the lumen of the tubules filled with granular material. In the pyramids, especially in the larger tubules, there is a remarkable desquamation of the epithelial cells. The lumina of the stripped tubules contain isolated epithelial cells, or large casts made of cubical cells, yellowish-brown detritus granules, leucocytes, and red blood-corpuscles. In the casts the cells stain well. The large bloodvessels are empty. The glomerulus capillaries contain parasites in moderate numbers, the capillaries of the labyrinths very few. In the pyramidal vessels, on the contrary, there are large numbers of the organisms, reminding one of the capillaries in the brain cortex or liver. Pigmented leucocytes occur in these vessels in moderate numbers. In the renal epithelial cells the characteristic malarial pigment does not occur, and in the glomeruli the pigment appears not to be in the cells. Many tubules in the pyramids contain greenish-yellow granules, like those described in other organs, and similar granules can occasionally be seen in the endothelial cells of the bloodvessels.

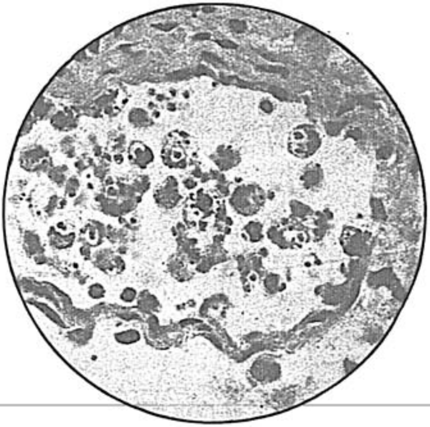
The right supra-renal body contains, in a large vein in the medulla, a thrombus having a structure like those in other organs.

Stomach. The bloodvessels of the submucosa are all distended with blood which often presents increase of leucocytes. A large vein contains a thrombus, almost filling the lumen, made up of leucocytes and an unusually large amount of fibrin. In the mucosa there is marked small cell infiltration between the tubules, and in the submucosa there is an infiltration along the small vessels. The intertubular capillaries contain large numbers of parasites and pigment masses. Very often there is complete filling of several adjacent capillary meshworks. Most of the pigment shows no trace of parasite (probably the effect of post-mortem maceration). In the large vessels, and in the thrombus, the conditions as to parasites, pigment, and phagocytes are as in other similarly affected parts. In a large vein I found one cell resembling a large splenic phagocyte, with several enclosures. It was in the middle of the lumen of the vein.

The slate-colored parts of the intestine show conditions like those in the stomach. The pigment showed especially well in teased fresh bits, where the capillary network in the villi was perfectly marked out by pigment.

Pancreas. The pancreas contained a few parasites in the capillaries, but no other changes of note. In examining that organ, however, I was struck by the large quantity of pigment in the loose fat around it, and was led in that way to examine the abdominal fat as far as possible. Besides the fat around the pancreas, I had preserved a good deal adherent to the adrenals and the stomach. Everywhere in this tissue I find the same peculiarities. In the first place there is an unusual fulness of the bloodvessels, resembling that in the bodies of persons dying of valvular lesions of long standing. There were, besides, interstitial hemorrhages. In all the blood in these parts, including the hemorrhages, there are quantities of parasites such as are found nowhere else except in the spleen. Every cross section of a capillary shows one or more parasites, and where the capillaries are cut lengthwise every one of the closely packed blood corpuscles can be seen to contain an organism. In the smaller veins the numbers are enormous, but in the larger veins the blood appears quite normal. Many of them are in the later stages, as in the other organs, but often small bodies can be seen in the red blood-corpuscles, taking a faint stain and containing very minute pigment grains, which appear to be bodies in an early period of development. In the larger veins are large numbers of leucocytes, and often thrombi, made up of leucocytes in a coarse fibrin network. The leucocytes contain pigment and parasites (see Fig. 5). They are large polymorphnuclear cells, with comparatively small nuclei, usually near the edge. They are not so large as the macrophages in the spleen. The parasites often lie in clear spaces in the protoplasm of the cells. The organisms in the phagocytes are all in the later stages of development, including that of separation of the spores. The latter cannot be recognized in the figure, but one parasite completely segmented can be recognized. The leucocytes do not exhibit a marked tendency to approach the walls of the vessels. The figure shows the nearest approach to that I could find, but neither here nor elsewhere is there evidence of phagocytism on the part of the endothelial cells.

FIG. 5.



Vein in abdominal fat, showing the phagocytes. In many leucocytes the bodies of organisms can be seen lying in vacuoles. In one parasite segmentation can be seen to have begun. There are many parasites in free red blood-corpuscles and in the plasma, some of which are segmented, but these do not show distinctly in the photograph. Hæmatoxylin. Apochromatic obj. 3 mm., oc. 4. × 640.

CLASSIFICATION OF THE PARASITES IN THIS CASE.—As I have stated in my former communication, the parasites encountered in this case seem to be identical with those described by Marchiafava and Celli and their pupils as the small plasmodium,[1] or the parasite of summer and autumn in Rome, and to which more specific names have been given by other writers. They agree, so far as one can determine by descriptions and without actual comparison, in the size of the fully-developed organism, their short cycle (about twenty-four hours), their lively motion, and the peculiarities of the spore figure and of the pigment (see Fig. 4).

THE PARASITES BEFORE AND AFTER DEATH.—In this case I hoped to be able to get some light on the question of the development of the organisms in the dead body. During the last hours many of the organisms were in the latest stages—that is, there were round bodies with central pigment, and segmented bodies. Had these continued their development they should all have disappeared within a few hours. Besides these there were many small bodies, almost uniform in size, and either entirely without pigment or containing only one or two of the finest grains. As the autopsy was made just twelve hours after death, it was to be expected that if further development had taken place only the half-grown parasites would be found—that is, small ones with scattered pigment grains. This, however, was not so. In blood from different organs examined at the autopsy, and in cover-glass preparations and hardened tissue, there are enormous numbers of sporulation figures and a few unsegmented but, judging from their size and pigment, almost ripe organisms (see Fig. 4). In splenic and in peripheral blood there are very small bodies, slightly larger than spores, apparently in the red blood-corpuscles. These are most probably the earliest intracellular forms. In one place only, in the red blood-corpuscles in the abdominal fat, are there small pale bodies (stained preparations) containing minute pigment grains. There seem to be plasmodia slightly more advanced in development than the spore-like ones in the spleen, and correspond approximately to what one would expect to find at that time in the finger blood had the process continued.

It seems, then, that the growth of the parasites was checked almost completely very soon after the patient's death. Whether this was due to lack of oxygen or to altered temperature, or to other causes, we can only conjecture.

REMARKS.—When we endeavor to trace the relation of the infecting organisms on the one hand to the clinical phenomena and anatomical changes as found post-mortem on the other, we find, even in a comparatively simple case like the foregoing, many difficulties. It is worth while to consider some of the possible sequences of cause and effect.

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[1] The use of the term plasmodium as the generic one for this organism is so much greater than that of all proposed substitutes taken together, that objections seem useless. The fact that the word is used as a technical term in biology can hardly lead to confusion, unless perhaps in the very beginning of investigations in the literature of malaria.

As the most direct result of the action of the parasites, we must consider a destruction of red blood-corpuscles and a corresponding anæmia (oligocythæmia). It is easy to understand the mode of production of this when we remember that the development of each parasite involves the destruction of a red blood-corpuscle. The extent of the destruction must vary widely in different cases, in many mild tertians being less than one per thousand in forty-eight hours, in some quartans even less. In a case like the one now reported, blood-counts are unreliable. I explained the high count in this case (6,000,000 per c.mm.)—which was paralleled in another case of malarial remittent, with a temperature of 106.2° F.—by a concentration of the blood mass, which, in view of the continued high temperature, the rapid breathing, the continual vomiting, and failure of absorption of water swallowed, is not difficult to understand. For reasons equally clear, estimations of the hæmoglobin in the acute stages of malaria have a possible source of error. The most plausible explanation of the blood after malarial attacks is that it is in a condition similar to that in post-hemorrhagic anæmia, with reduction of the number of red corpuscles and hæmoglobin in equal proportions, and during recovery the count increasing more rapidly than the hæmoglobin, with nucleated red corpuscles appearing. The early appearance of the nucleated red corpuscles is shown in my own case.

An accurate estimation of the proportion of parasites to corpuscles could not be made in my case. In finger blood, proportions of one to five or six were not uncommon, and sometimes the proportion was even greater. But in other preparations there were smaller numbers of parasites. In many internal organs, however, the relative numbers of parasites must have been very great. It is probably safe to assume that in the last day there was a proportion throughout the blood as a whole of not less than one to five, involving the destruction of that proportion of red corpuscles in twenty-four hours. This is not incredible, for other observers (Mannaberg, *Die Malaria-Parasiten*, p. 154) have reported cases in which the proportion could not have been less.

Such a proportion indicates an enormous power of development on the part of the organisms. It is not enough to assume that a large number of parasites have been taken in, which has sometimes been supposed to be the cause of pernicious attacks. It is known that in ordinary cases of malaria destruction of a part of each new generation of parasites takes place. In a case in which this is not great, or is absent, the natural increase of the bodies would soon produce a number equal to that in even so severe a case as the one now reported.

The peculiar conditions leading to unusual development of the spores may have some connection with the greater resistance to quinine present in such cases.

Clinically, the anæmia in my own case may be said to have been expressed in the dyspnœa (which also probably had other causes) and the thirst. In another case of pernicious malaria I had a striking example of the latter symptom. The case was one of algid pernicious, with a temperature of 95° to 97° F., in which the patient begged piteously for water. This has been supposed to indicate an internal high temperature. Asking the man, whose mind was perfectly clear, if he had fever, he said "No, but I am so dry." In a few hours he was dead, asking for water (which he got, and could swallow and absorb) to the last; but the temperature in internal organs, half an hour after death, was only 98° F.

But anæmia does not explain all the clinical phenomena of this or any other case of acute malaria. In my own case there are lesions in abundance, but it is not easy to ascribe to each one its part in the production of the symptoms or the relation of the parasites to the lesions.

There is a probable effect of the parasites aside from the anæmia which we must consider, namely, the formation of toxic substances. In the growth of the parasites and in the digestion of the red blood-corpuscles it can hardly be doubted that toxic substances are produced. What these are or how they act we cannot say. It is reasonable to suppose that the characteristic phenomena of the paroxysms are largely due to the action of the hypothetical poisons on the nervous system. It might be urged that this theory of the paroxysms, which is of course not new, is weakened by the fact that in the more severe malarial infections some of the phenomena are not so strikingly exhibited as in mild cases. It is to be remembered, however, that in the severe infections substances may be formed in unusual quantities which have an inhibitive action on certain phenomena of the paroxysms. Moreover, it cannot be doubted that temporary or permanent disposition has much to do with the clinical features of malarial paroxysms.

The most important factor, however, in the causation of the atypical attacks of malaria is perhaps the inflammation which is so marked in certain organs. It is not difficult to see how the difference between an intermittent and a remittent, or even continued fever, might depend on the existence in the one case of a gastritis or hepatitis.

The possibility of an action of toxic substances on the nervous system cannot profitably be considered in connection with my own case. The method of hardening employed makes it impossible to say positively that there were no degenerations of the nervous tissue. Some nervous symptoms, like delirium, were not so marked in this case as often happens in pernicious malaria, even in less severe cases, but the possibility of toxic substances acting on the centres of the medulla must not be forgotten, the more so as we cannot find vascular changes to account for the dyspnœa and other symptoms (respiratory death?) which might have been wholly or in part of medullary origin.

The necrotic alterations in certain other organs can hardly be looked upon as anything but the results of toxic substances. I refer especially to those in the liver and kidney. The alterations in the stomach were probably also originally toxic, but in the case of this organ other influences may have assisted. The other changes in these organs, vascular fulness, small-cell infiltration, etc., would seem to have been partly reactive, due to the necrosis, though they might also be ascribed with some reason to the same causes as those which produced necrosis.

Some peculiarities of the parenchymatous lesions deserve emphasizing. In the liver the areas of interstitial inflammation and necrosis do not coincide. The infiltration does not seem to involve, therefore, a preceding necrosis. It is noteworthy that judging from the forms of cells there is no tendency to suppuration.

But while this one case, in which other possible causes seem absent, shows that malaria can give rise to interstitial hepatitis, examinations in other cases indicate that the process does not always occur. In the liver from the case of algid pernicious there are small areas of necrosis, but no infiltration. In a case with death from ruptured spleen there is neither necrosis nor infiltration in the liver.

While the alterations in the cortex of the kidney seem toxic, the changes in the tubules of the pyramids are so different that it may be questioned whether they are not due to local circulatory disturbances, especially in view of the condition of the blood in the capillaries of those parts. No matter how caused, the desquamation gives a simple explanation of the hæmaturia, an explanation which of course cannot be applied to other cases without confirmatory observations.

The parenchymatous changes in the stomach and the similar but less severe alterations in the intestines, as is well known, do not occur to the same extent in all cases. In the algid case mentioned before there was marked chronic gastritis, but no recent change. It may well be that the anæmia accompanying the chronic disease had some influence on the process.

It is difficult to estimate the precise anatomical and clinical importance of thrombosis, which occurred most frequently in the brain cortex. In the latter it is not so marked as it has been apparently in some other reported cases. Though it probably had some connection with some of the nervous symptoms observed, it does not seem, from its localization, as if it could have had any bearing on the more important symptoms, especially the dyspnœa, the temperature, or the pulse.

Certain phenomena of malaria are due probably to the peculiarities of the localization of the organisms. This, from the little we know of the subject, certainly varies in different cases. In my case it was most marked in the spleen, liver, brain, and kidney, and last, but not least, in the abdominal fat. The localization of the malarial parasites, like that of other blood parasites, is opposed to our ordinary ideas of the circulation, but the fact is more remarkable in malaria in that the parasites are for the most part within the passive red blood-corpuscles. That blood parasites in general tend to accumulate in parts where the circulation is slow is well known, and that infected or diseased red blood-corpuscles tend to accumulate in certain organs with slow circulation, like the liver and spleen, is also known, but these facts do not explain the whole matter. In the case of the abdominal fat the hyperæmia would offer favorable conditions for stagnation, but the cause of the hyperæmia cannot be easily explained. It is, perhaps, necessary to say that the abdominal congestion was not due to chill, as there was none. Still less could it be of post-mortem origin.

Another fact which seems to have some connection with the peculiar localization of the parasites is the remarkable distribution of the leucocytes. The proportions of the various forms of leucocytes indicate that there was an unusual production of those cells, which may be explained by an irritation of lymphoid tissues, but owing to the irregular distribution, efforts to count them were even less successful than in the case of the red corpuscles. They are present in greatly increased proportion in the capillaries, and often, but not always, where parasites are especially numerous. They are also present in remarkable numbers throughout the congested abdominal fat, as shown by Fig. 5.

The latter facts might be interpreted as indicating that the leucocytes go where there are the greatest numbers of parasites. But many of the increased number of leucocytes in those places are cells that do not act as phagocytes, so that it seems more rational to assume that local conditions of the circulation, leading to stasis, are the important factors in the accumulation of both parasites and white corpuscles.

PHAGOCYTES AND PHAGOCYTOSIS.—In this case the enclosure of parasites is extraordinarily frequent, as a reference to Fig. 5 will show. In blood taken from the finger at 8 P.M., 10 per cent. of the leucocytes are phagocytes, there being large and small polynuclear cells in the relative proportions of 6 and 4 per cent. In the finger blood the phagocytes seem to be leucocytes such as occur normally in blood. In the liver, the spleen, and bone-marrow there are larger cells. The most remarkable are those which occur in such large numbers in the spleen. They are similar to, but usually larger than the large cells found in the spleen in other infectious diseases, especially typhoid fever and certain cases of pyæmia. The origin of these cells is obscure. From their appearance an endothelial origin might be supposed, but nowhere in my own case is there evidence of such an origin. Notwithstanding most careful search I can find no sign of phagocytosis in endothelial cells *in* *situ*, which is claimed by Metchnikoff[1] and his pupils as being common in many conditions, including malaria. There is also no swelling and no apparent desquamation of endothelial cells. In G. P., I cannot find pigment in the liver outside of the vessels, but in cases of longer duration I find it occasionally in the cells of Kupffer, claimed as of endothelial origin by Metchnikoff,[2] but not even in those cases in the endothelial cells in the inner surfaces of the vessels. This question is discussed from another point of view later.

In regard to the enclosures of the phagocytes, the commonest is pigment, especially pigment of the form which is present when the parasites undergo segmentation. Next in frequency are parasites. These are in the later stages, especially the stage of segmentation. It seems to me, though the point is a difficult one to decide, that the bodies in the phagocytes, on the whole, are in an earlier stage of development than those not enclosed. This may be due to the fact that those free in the blood continued to develop after the others were swallowed. But as parasites when swallowed in an active condition continue to show signs of life for some time, as many observers have noticed, it seems more likely that the enclosed parasites in my case were dead or dying when swallowed. In other words, I think that the work of the phagocytes in such cases is not essentially different in its objects and method from that exhibited in regard to any inert foreign material in the vessels. Certainly if phagocytism were directed to plasmodia alive and active, we could never have such a large number of parasites in the blood as occurred in this case, for in the beginning even the circulatory phagocytes must be present in greater number than the parasites, while the endothelial cells also have good opportunities for acting on them. Once the parasites are paralyzed or killed, either by drugs given for the purpose or by something formed in the body, there would be nothing left for certain cells to do but enclose them for further disposition.

THE MALARIAL PIGMENT.—Since the excellent work of Arnstein,[3] we have known that the malarial pigment originates in the red blood-corpuscles, and so might contain iron, but at present we do not know whether it really does contain iron, although various writers make positive statements pro and contra. For years, on account of its color, malarial pigment has been called melanin. But as the real nature of various other so-called melanins has been made known, there is a tendency on the part of chemists to restrict the use of the word to certain pigments of known composition, and probably different from malarial pigment, though pathologists have not shown a tendency to observe the distinction. Nothing short of an ultimate analysis will enable us to properly classify or name the malarial pigment; and such an analysis, with suitable material, should not offer insuperable obstacles. The micro-chemical tests so far available cannot decide as to the presence or absence of iron, as the results of various observers ought to show. Knowing the impossibility of settling the question, but hoping to arrive at some explanation of the contradictory statements of others, I made an extensive series of examinations, and feel that the results are worth recording.

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[1] Leçons sur la Pathologie comparée de l'Inflammation.

[2] Loc. cit., p. 163 et seq.

[3] Virchow's Archiv, 1874, Bd. lxi.

In order to test various methods, I used the liver and kidney of a case of pernicious anæmia from the collection of the Leipzig Pathological Institute. All the specimens had been hardened in strong alcohol. They were cut in paraffin and fixed on cover-glasses by heat. They came in contact with iron only in the process of cutting.

I began with ammonium sulphide, but had to give it up as unsuitable. It gave the iron reaction in certain of the yellow globular particles resembling hæmoglobin, in the vessel walls, and in the large phagocytes of the spleen. It slowly dissolved the malarial pigment, decolorizing a section completely in from twenty minutes to an hour. Afterward there was a black amorphous precipitate, due probably to the evaporation of the reagent. The solubility of the pigment in ammonium sulphide had been observed before.[1] Evidently with a reagent so powerful as ammonium sulphide but little could be expected, and after determining the facts mentioned I took up the Berlin and Turnbull's blue tests. In using these I found after trying various methods that the modification used by M. B. Schmidt[2] gave the best results. It is as follows: A two per cent. solution of potassium ferrocyanide is poured in a dish and pure hydrochloric acid added in the proportion of one per cent. The sections are placed in this, and in case the reaction is positive soon become more or less blue. It is advisable to follow the reaction under the microscope with a low-power objective. After the maximum intensity of color is obtained the section should be washed in distilled water and can then be mounted or can be stained and then mounted. For staining I use lithion carmine, though, of course, any contrasting stain could be used. If the staining be done first, as is sometimes recommended, no matter how carefully the solutions are filtered, a number of minute cotton fibres and more or less granular material will adhere to the sections and give the iron test, which is extremely delicate.

The pigment in the parasites, including the finest grains, never gives the blue reaction. The same is true of free pigment, or pigment in phagocytes which can be recognized as of parasitic origin. This, of course, does not prove that iron is not present, but only that it is not present in a form which responds to the test.[3] But in the course of the observations I obtained results which may go to explain the statement of some, that the pigment gives the iron test. The yellowish globules already mentioned all give the Berlin-blue reaction distinctly, but in different degrees of intensity. They occur in almost all organs, though in most places sparingly. They can be found in the endothelial cells of the vessels, sometimes in the vessels, among the blood corpuscles. In the kidneys they are present also in the epithelial cells, but here not all the yellow particles, even in the same cells, give the reaction. In the spleen there is a diffuse blue stain from fine particles which give the test. In the macrophages, among the other enclosures, fine blue particles appear. The liver shows three kinds of pigment: the malarial pigment, the orange-yellow pigment, common in that organ, and yellow granules similar to those in other organs. Of the three, only the latter give the blue reaction. In my case these granules are present in great number, being almost as numerous as in the case of pernicious anæmia. In the case of rupture of the spleen there are almost as many, but in the algid case there are comparatively few. The casts in the renal tubules do not give the reaction at all, a result which surprised me, but which was very thoroughly controlled. (In these casts there was no malarial pigment.)

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[1] Kiener: Cited by Mannaberg, Die Malaria-Parasiten, p. 26.

[2] Virchow's Archiv, Bd. cxv. p. 402, note.

[3] See the excellent remarks of E. Neumann on this subject, Virchow's Archiv, Bd. cxvi. p. 318.

There is, then, in malaria an unusual deposit in certain organs of a material which gives an iron reaction, though the malarial pigment proper does not do so. There is a very simple explanation of the origin of this material, which has occurred to others. The explanation is as follows: The true malarial pigment is an excrementitious substance formed by the digestion of the red blood-corpuscles. In the development of the parasite the corpuscle infected is not always completely digested, but a narrow ring or part of a ring is left. Even in the case of the larger parasites of tertian or quartan fever, which, when full-grown, are as large as or larger than a red corpuscle, complete digestion of the red cells does not always occur. In the case of the smaller parasites of pernicious fever a comparatively large part of the red corpuscles must be left over after the development of the relatively small organism. But the relics of the affected cells must be unable to carry on the ordinary functions of blood corpuscles. Evidently they must follow the course of worn-out red corpuscles, and some of their constituents be used over again or excreted. For the former purpose they will be taken up by various cells, especially by cells in the spleen, the liver, and the bone-marrow. According to this view, the iron-reacting granules in the various cells are derived from the débris described, the hæmoglobin having been so altered as to give the iron reaction. It is interesting to see that this storing-up takes place to a greater extent in some organs and some cells than others, just as occurs under ordinary circumstances, and in my cases is most marked in the great "magnet" of Kobert, the liver. Part of the hæmoglobin may also be excreted by the kidneys.

In my cases this seems to have been slight, and the results of the iron tests in the kidneys were so different from those of Stieda[1] that it would seem that storing-up and excretion vary in different cases.

There are some other possibilities which may be mentioned. One is that the iron-reacting granules are derived from the malarial pigment, which has been altered by the cells containing it. Against this view is the fact that in those cells in which the blue granules are most numerous the ordinary non-reacting pigment cannot be found. The malarial pigment must ultimately be worked up in some way, or eliminated, because in examinations of old cases of malaria there is much less pigment than one would expect to find; but even in these cases the unmistakable pigment left in the connective tissue gives no iron reaction.

Another possibility which may be suggested is that part of the dark pigment occurring in the leucocytes has been formed there out of hæmoglobin remnants. There is no evidence of this, however, and the malarial pigment, from all we know about it, seems to differ from all the other pigments formed by or from the blood.

SYPHILIS OF THE EPIDIDYMIS.

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During my term of service at the City Hospital, just drawing to a close, it has been my fortune to treat several men whose histories are not without interest, and in relating them in connection with some previous observations, I will take occasion to speak of those conditions of the epididymis in syphilitics, which are too commonly passed over with the comprehensive diagnosis "Syphilitic testicle." There are, as is well known, instances in both early and late syphilis, in which the epididymis is alone involved, while the globe of the testis remains free, but too little attention has been paid to them, and they are usually passed over in the text-books with either slight comment or are wholly neglected. I do not wish the not infrequent combination orchi-epididymitis to enter into this discussion, nor will I dwell upon those instances in which both globe and epididymis are coincidently affected, and the epididymis is simply indurated and enlarged after the testis has softened and regained its normal condition.

In support of my proposition that authors have comparatively little to say about the epididymis as an independent seat of specific involvement, I quote from several different sources the following sentences:

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[1] Centralblatt f. allg. Path. u. path. Anat., 1893, p. 321.